REMARKS/ARGUMENTS

The Pending Claims

Claims 5, 8, 10-12, 18, 20, and 32-35 are pending and are directed to a method of enhancing an immune response in a subject (claims 5, 8, 10-12, 32, and 34) and a method of treating a subject with a condition comprising a deficiency of at least one of memory B cells and plasma cells (claims 18, 20, 33, and 35).

Amendments to the Claims

Claims 5 and 18 have been amended to recite that the composition comprises a variant of the amino acid sequence of SEQ ID NO: 1 with 1-5 amino acid substitutions, deletions, or additions. Such features are recited in claims 34 and 35. No new matter has been added by way of these amendments.

Summary of the Office Action

The Office rejects claims 5, 8, 10-12, 18, 20, and 32-35 under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description.

The Office rejects claims 5, 8, 10-12, 18, 20, and 32-35 under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement.

Reconsideration of these rejections is hereby requested.

Discussion of the Written Description Rejection

The Office contends that the specification does not provide adequate written description for the genus of IL-21 variants. The Office contends that the specification does not disclose regions or domains of the protein that are essential to bind the IL-21 receptor resulting in the claimed physiological effects. In particular, the Office contends that the specification does not disclose what amino acids are in the active site, the binding pocket, or the hydrophobic core of the protein.

The pending claims recite an IL-21 polypeptide comprising SEQ ID NO: 1 or a variant of SEQ ID NO: 1 with 1-5 amino acid substitutions, deletions, or additions. The

variant retains the ability to bind to the IL-21 receptor and produce the same physiological effect produced by binding of the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 to the IL-21 receptor. The amino acid sequence of SEQ ID NO: 1 contains 160 amino acids. Since the variant contains at most 5 mutations, the variant has *more than 96.8% identity* to SEQ ID NO: 1.

As discussed in the previous Reply to Office Action, the specification describes variants for use in the invention at, for example, page 31, lines 1-26. In particular, the specification cites to U.S. Patent Application Publication 2003/0003545 (Ebner et al.) for the disclosure of variants that differ from IL-21, but retaining the essential properties thereof. Ebner et al. discloses conserved regions of IL-21 polypeptide in Figures 1, 4, 6A-B, and 7, and Tables I-III. Furthermore, Ebner et al. discloses regions of identity between IL-21 and other interleukins in Figures 3A-C. Thus, regions of IL-21 polypeptide that should not be mutated were known in the art. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

Furthermore, assays to determine suitable variants are described in the specification or known in the art. For example, the claims require that the IL-21 variant produces the same physiological effect produced by binding of the IL-21 polypeptide to the IL-21 receptor. The specification describes that the IL-21 polypeptide activates the JAK/STAT signaling pathway (see, e.g., page 8, line 30, through page 9, line 5), induces differentiation of B cells and B cell progenitors into memory B cells and/or plasma cells (see, e.g., page 9, lines 6-20), induces expression of mRNA for Blimp-1 and Bcl-6 (see, e.g., page 53, lines 27-29), and inhibits expression of Pax5 mRNA (see, e.g., page 53, lines 27-30). Assays to determine if an IL-21 variant produces the above-described effects (e.g., real-time PCR) are known in the art and are described in the specification at, for instance, page 41, line 19, through page 44, line 16; and Examples 3-5.

Accordingly, based on the teachings in the specification and what was known in the art, one of ordinary skill in the art would have recognized that Applicants had possession of an IL-21 polypeptide variant *with greater than 96.8% identity* to SEQ ID NO: 1 for use in the inventive methods.

Discussion of the Enablement Rejection

The Office maintains the enablement rejection of the pending claims. This rejection is traversed for the following reasons.

A. The Genus of IL-21 Polypeptide Variants is Enabled

The Office contends that the claims are not enabled for the genus of IL-21 polypeptide variants. As discussed above, the claims recite an IL-21 polypeptide comprising SEQ ID NO: 1 or a variant of SEQ ID NO: 1 with 1-5 amino acid substitutions, deletions, or additions. Accordingly, the variant has *greater than 96.8% identity* to SEQ ID NO: 1.

Furthermore, the claims require that the variant retains the ability to bind to the IL-21 receptor and produce the same physiological effect produced by binding of the IL-21 polypeptide to the IL-21 receptor. The specification describes that the IL-21 polypeptide activates the JAK/STAT signaling pathway (see, e.g., page 8, line 30, through page 9, line 5), induces differentiation of B cells and B cell progenitors into memory B cells and/or plasma cells (see, e.g., page 9, lines 6-20), induces expression of mRNA for Blimp-1 and Bcl-6 (see, e.g., page 53, lines 27-29), and inhibits expression of Pax5 mRNA (see, e.g., page 53, lines 27-30). Assays to determine if an IL-21 variant produces the above-described effects (e.g., real-time PCR) are known in the art and are described in the specification at, for instance, page 41, line 19, through page 44, line 16; and Examples 3-5.

Additionally, the specification describes variants for use in the invention at, for example, page 31, lines 1-26, and cites to U.S. Patent Application Publication 2003/0003545 (Ebner et al.) for the disclosure of variants that differ from IL-21, but retaining the essential properties thereof. Ebner et al. discloses conserved regions of IL-21 polypeptide, such that one of ordinary skill in the art would have recognized regions of IL-21 polypeptide that should not be mutated in an IL-21 variant.

For the above-described reasons, variants of SEQ ID NO: 1 with 1-5 amino acid substitutions, deletions, or additions (which have *greater than 96.8% identity* to SEQ ID NO: 1) are fully enabled by the specification.

B. The *Ex Vivo* Methods Are Enabled

The Office maintains that the specification does not provide sufficient guidance for inducing an immune response against a viral infection. The Office contends that Applicants have not provided evidence supporting how an immune response against a viral infection is effective merely by a humoral response (e.g., a memory B cell and a plasma cell) as viruses are intracellular pathogens and an effective response against intracellular viral pathogens requires cell-mediated immunity (processing and association of the viral antigen with the MHC Class I molecule on APC cell surface for activation of T cells).

Applicants again note that claims 5, 7, 10-12, 32, and 33 are directed to a method of *enhancing* an immune response by administering one or more of a memory B cell and the plasma cell produced *ex vivo* to the subject. The claims do not preclude that the subject experiences a cell-mediated immune response against an antigen (e.g., viral antigen). Nor do the claims recite that one or more of a memory B cell and the plasma cell *induces* an immune response. Rather, the claims recite that the addition of the memory B cell and plasma cell *enhances* (i.e., improves) an immune response in a subject.

As discussed in the previous Reply to Office Action, viruses can be extracellular in the course of infection. Therefore, viral antigens can be extracellular antigens against which an immune response in the form of antibodies (e.g., against antigens of the viral envelope) would be beneficial. Indeed, success in clinical trials using antibodies against the viral envelopes of hepatatis C virus and HIV has been reported (see, e.g., Joos et al., *Antimicrob. Agents Chemother., 50(5)*: 1773-1779 (2006); Armbruster et al., *J. Antimicrob. Chemother., 54*: 914-920 (2004); and Galun et al., *J. Hepatol., 46(1):* 37-44 (2007); submitted herewith).

The use of antibodies to inhibit virus infection is a well-established technology. For example, Mascola et al. and Baba et al. reported the protection afforded by the introduction of neutralizing antibodies against HIV infection in the February 2000 issue of the journal *Nature Medicine* (see, Mascola et al., *Nature Medicine, 6(2)*: 207-210 (2000) and Baba et al, *Nature Medicine, 6(2):* 200-206 (2000); submitted herewith).

Thus, based on the description in the specification and what was known in the art at the effective filing date of the application, one of ordinary skill in the art would expect that the administration of one or more of a memory B cell and the plasma cell can serve to

enhance an immune response (e.g., a cellular-mediated immune response against a viral antigen).

The specification discloses that a population of cells (e.g., B cell progenitors) that have been isolated from a subject can be contacted with IL-21 polypeptide or variant thereof, which results in the differentiation of the B cells into plasma cells and/or memory cells, which are then isolated (see, e.g., page 34, line 18, through page 35, line 3; and Examples 3-5). Furthermore, the specification discloses the administration of the isolated memory B cells and plasma cells to the subject to *enhance* an immune response (see, e.g., page 34, line 18, through page 35, line 3). Since antibody production (e.g., by plasma cells) is an essential element of the immune response, one of ordinary skill in the art would recognize that the inventive methods would be effective in *enhancing* an immune response in a subject.

Claims 18, 20, 34, and 35 recite a method for treating a subject with a condition comprising a specific deficiency of at least one of memory B cells and plasma cells by administering at least one of the memory B cell and plasma cell to the subject. As described above, the claims do not preclude that the subject experiences a cell-mediated immune response against an antigen (e.g., viral antigen). Rather, the claims recite that a deficiency of at least one of memory B cells and plasma cells is remedied by specifically administering that which is deficient (i.e., at least one of memory B cells and plasma cells).

Accordingly, based on the teachings in the specification and what was known in the art, one of ordinary skill in the art would have recognized how to perform the inventive methods without undue experimentation and with an expectation of success.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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